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Filing Date	November 8, 1999
First Named Inventor	Chen et al.
Art Unit	1616
Examiner Name	Landau, Sharmila Gollamudi
Attorney Docket Number	141-594

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
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- ☐ Amendment/Reply
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  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
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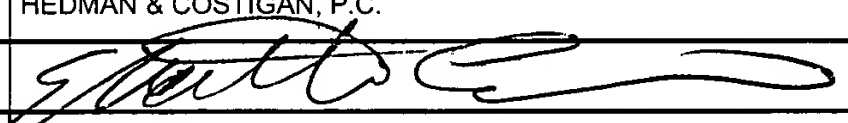
Signature			
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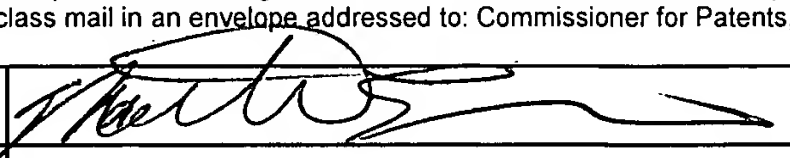
Signature			
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Chih-Ming CHEN, et al.

Serial No.: 09/435,576 Group Art Unit: 1616

Filed : November 8, 1999 Examiner : Sharmila S. Gollamudi

For : HMG-COA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION

New York, NY 10036
November 27, 2007

Mail Stop Appeal Brief - Patents
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REPLY TO EXAMINER'S ANSWER

Sir:

Appellants submit the present brief in response to the Examiner's Answer, dated October 29, 2007 and in support of the Notices of Appeal filed on November 21, 2005 and February 28, 2007, the Brief on Appeal filed on February 28, 2007 and the Reply to Examiner's Answer filed on July 24, 2007 and Appellants Amended Brief on Appeal filed on July 24, 2007 in the above-identified application. Reversal of the Examiner's rejections respectfully is requested based on the following arguments. Appellants believe no fee is required for submission of this brief. Notwithstanding, the Commissioner is hereby authorized to charge Deposit Account No. 08-1540 for any fee required. A duplicate copy of this sheet is enclosed.

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Martin P. Endres Reg. No. 35,498

STATUS OF CLAIMS

Claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are pending in this application, and no amendments have been made since the final rejection dated July 21, 2005. The rejection of these claims is appealed herein.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are whether:

A) Claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are anticipated under 35 U.S.C. § 102(b) in view of Alberts et al., United States Patent No. 5,376,383 (hereinafter "the Alberts reference");

B) Claims, 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are obvious under 35 U.S.C. § 103(a) in view of Chen et al., United States Patent No. 5,837,379 (hereinafter "the Chen et al. reference") by itself or in view of Cheng et al. (Evaluation of Sustained/Controlled Release Dosage Forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (1993), 10: 1683-1687 (hereinafter "the Cheng article"); and

C) Claims 1-13, 18, 19, 21, 22, 25-47, 76-77 and 80 are unpatentable under the judicially created doctrine of obviousness-type double patenting in view of claims 1-12 of United States Patent No. 6,485,748 and Remington's Pharmaceutical Science (18th Edition, 1990).

REPLY ARGUMENT

The present matter is an example of not seeing the forest for the trees. Specifically, it appears that the invention has been lost in a mass of data and verbiage.

As recited in the pending claims the present invention is a controlled release dosage form that provides a mean time to maximum plasma drug concentration (T_{max}) of 10 to about 32 hours. The drug is an alkyl ester of hydroxyl substituted naphthalenes, i.e, a HMG-CoA reductase inhibitor or statin drug such as lovastatin or simvastatin. What is unique and unexpected about such a composition is that the amount of drug in a patient's blood after administration is higher compared to the amount of drug in a patient's blood after administration of a comparable immediate release form.

For example, when a 40 mg lovastatin immediate release dosage form and a 40 mg lovastatin controlled release dosage form of the present invention are administered to a human patient, the concentration of lovastatin, as measured by AUC (area under the concentration-time curve) was higher for the present invention than for the immediate release dosage form. This unique pharmacokinetic property is summarized in Table 9 on page 48 of the present application. Table 9 shows that, depending upon the time of administration, the AUC for lovastatin in a patient's blood can be 1.41 to 1.91 times higher with the present invention compared to a comparable immediate release dose of lovastatin. This pharmacokinetic property is completely unexpected because the AUC for both dosage forms is expected to be similar due to the fact that the same amount of lovastatin was administered to the patients.

This unexpected increase in the amount of drug in a patient's blood allows more drug to be available to the patient and therefore allows similar therapeutic effects with lower amounts of drug being administered. In the case of statin drugs such as lovastatin, the present invention has the unexpected benefit of reducing the concentration levels of the active acidic metabolite in the patient's blood. Keeping the concentration levels of the active acidic metabolite low is important because high concentrations in a patient's blood can be toxic to the patient's skeletal muscles. All these unexpected benefits are summarized in Tables 6-12 and on pages 45-55 of the present specification.

REPLY TO ANTICIPATION REJECTION

In the Examiner's Answer, the Examiner maintained the anticipation rejection based upon Example 10 of the Alberts reference and indicated that Appellants' evidence indicating a lack of anticipation is not sufficient to overcome the rejection.

Although Appellants believe the prior arguments are sufficient to overcome the anticipation rejection, Appellants respectfully direct the Board's attention to the Cheng article which the Examiner has relied upon to reject the pending claims under 35 U.S.C. § 103(a).

The Cheng et al. article discloses the *in vivo* and *in vitro* test results of a number of controlled, sustained and modified release dosage forms of lovastatin and simvastatin. One dosage form of particular interest is SRT 14 which is described on page 1683 as a swelling sustained release matrix. The *in vitro* data for SRT 14 is presented in Figure 2 on page 1684 of the Cheng article and indicates that about 90% of the lovastatin is released in about 18 hours.

The SRT 14 dosage form is similar to Example 10 of the Alberts reference which the Examiner relies upon for the anticipation rejection. Example 10 of the Alberts reference is also a swellable matrix dosage form that releases about 85% of the lovastatin in 18 hours.

Table II on page 1685 of the Cheng article indicates the T_{max} for SRT 14 is 2.3 hours. This is vastly different from the T_{max} of 10 to about 32 hours as recited in the pending claims. In addition, the Cheng et al. article states:

> Although lovastatin was released *in vitro* from either SRT 8 and SRT 14 in a sustained-release fashion (Fig. 2), the plasma concentrations of total HMG-CoA reductase inhibitors in dogs receiving lovastatin in SRT 8 or SRT 14 were not much different from those receiving the same dose of lovastatin in CT (Table II and Fig. 3). These results indicate that SRT 8 and SRT 14 formulation for lovastatin do not perform *in vivo* as one would expect based on the *in vitro* results; nor do they provide plasma profiles (Fig. 3) that are protracted. Thus, the *in vitro* release profile does not predict the *in vivo* performance of these sustained-release formulations of lovstatin in the dog.

This data from the Cheng article clearly indicates that *in vitro* data cannot be used to predict the *in vivo* properties of a sustained release lovastatin dosage form and especially a swellable matrix dosage form such as that described in Example 10 of the Alberts reference. Because the Examiner's anticipation rejection of the pending claims is based upon *in vitro* release data in the Alberts reference and not actual *in vivo* testing, it is respectfully submitted that the anticipation rejection is improper because the evidence of record shows that a T_{max} of about 10 to 32 hours as recited in the pending claims is not always and necessarily obtained from a

sustained release lovastatin dosage form that release about 90% lovastatin in 18 hours during *in vitro* testing. Appellants respectfully requested that the rejection of the claims as being anticipated by the Alberts reference be withdrawn based upon the data of record, and in particular the data for SRT 14 in the Cheng et al. article.

REPLY TO OBVIOUSNESS REJECTION

In the Examiner's Answer, the Examiner maintained the rejection of the pending claims under 35 U.S.C § 103(a) as being obviousness in view of the Chen et al. reference by itself or in view of the Cheng et al. article. In addition to the arguments of record, Appellants respectfully submit that the rejection should be reversed because the Chen et al. reference does not disclose a controlled release statin formulation that exhibits a T_{max} of 10 to about 32 hours as recited in the pending claims.

It is Appellants' understanding that the Examiner agrees that the Chen et al. reference is not an anticipatory reference because there is no actual example that employs a statin drug and, more importantly, no actual disclosure of a sustained release statin dosage form that exhibits a T_{max} of 10 to about 32 hours as recited in the pending claims. It is Appellants' further understanding that the Examiner's rejection is based upon the similarity between the Examples of the Chen et al. reference and the examples of the current specification. Based upon these facts, it appears to be the Examiner's position that the substitution of a statin drug for the drug nifedipine in the prior art examples will inherently result in the presently claimed invention.

If the foregoing understanding of the Examiner's rejection is correct, Appellants respectfully submit that the rejection is improper under the current law. Specifically, the courts have stated that it is improper to based an obviousness rejection on an inherent property of the prior art. *In re Spormann and Heinke,* 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966) (wherein the Court stated: "That which is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). See also: *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (wherein the Court repeated the aforementioned quote from In re Spormann and Heinke) and *In re Newell,* 891 F.2d, 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989) (wherein the Court stated: [A] retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of various elements in the particular claimed combination...It is well established that in deciding that a novel combination would

have been obvious, there must be supporting teaching in the prior art. 'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.'" citations omitted).

Therefore, if the Examiner is suggesting that the Chen et. al reference renders the pending claims obvious because the substitution of lovastatin or other statin drug for nifedipine in the prior art dosage form will "inherently" result in a T_{max} of 10 to about 32 hours, such a rejection is improper. As clearly established by the above-cited cases, an obviousness rejection cannot be predicated upon inherency.

Notwithstanding the foregoing, Appellants respectfully submit that the Examiner's rejection of the pending claims under 35 U.S.C. § 103(a) should be reversed because an individual of ordinary skill in the art, when reviewing the Chen et al. reference and the Cheng article, would be very cognizant of the statement in the Cheng article that *in vitro* data does not predict *in vivo* performance. In light of this unambiguous statement, an individual of ordinary skill would not expect that the substitution of a statin drug for nifedipine in the prior art formulations would necessarily produce a dosage form with a T_{max} of 10 to about 32 hours as recited in the pending claims.

Appellants further submit that the pending claims are not obvious in view of the teachings of the Chen et al. reference alone or combined with the Cheng article because of the surprising and unexpected results Appellants obtained for a sustained release statin dosage form that exhibits a T_{max} of 10 to about 32 hours. As explained above and demonstrated by the *in vivo* testing reported in Tables 6-12 of the present specification, a statin dosage form that exhibits a T_{max} of 10 to 32 hours results in a much higher drug concentration in the body and a lower peak level of the acidic metabolite than a comparable immediate release dosage form. There is no disclosure or suggestion in the Chen et al. reference or the Cheng article that extending the T_{max} to 10 to about 32 hours as recited in the pending claims will result in the increased drug plasma concentration.

In this regard, Appellants note that the Examiner stated for the record "that Cheng teaches a controlled release device (CRS14) formulation providing a **Tmax of 7.5 + 1.2 hours (standard deviation 8.7 hours and Appellant claims about 10 hours)** for an 80mg lovastatin oral dose." Examiner's Answer at page 24 (emphasis in original). However, the Examiner is improperly using the standard deviation as the standard error of the mean. "Standard deviation"

measures the variability between individual subjects in the data – it is not a measure of error for the average. In order to determine the error for the average, one must divide the standard deviation of the individuals by the square root of N, where N is the sample size. That is, averages are less variable than the individual subjects who make up the average.

Therefore, Cheng actually teaches a T_{max} of 7.5 + .49 = 7.99, not 8.7 as the Examiner alleges. In this regard, the "+ 1.2" that Cheng teaches is not an actual unit of time but rather a standard deviation.[1] Therefore, in order to convert the standard deviation number into actual time, the following formula must be used:[2]

$$S_{\bar{X}} = \frac{S}{\sqrt{N}}$$

Taking S=1.2 and N = 6, $S_{\bar{X}}$ = ~0.49 hours. Therefore, the Cheng article's "7.5 + 1.2" really equals 7.5 + .49 = 7.99 hours. 7.99 hours cannot be said to read on 10 hours as claimed by the present claims.

Further, the pharmacokinetic data reported in Tables II and V of the Cheng article suggests[3] that there would be no increase in drug concentration following the administration of a controlled, sustained or modified release statin dosage form. Specifically, the AUC ratios reported in Tables II and V of the Cheng article compare the AUC of an immediate release statin dosage form (designated CT) with controlled, sustained and modified release dosage forms that exhibit a T_{max} of 7.5 hours or less. The reported AUC ratios are 1.03 or less suggesting that there is no increase in drug plasma concentration.

Based upon the unexpected results of a sustained release statin dosage form that exhibits a mean T_{max} of 10 to about 32 hours, it is respectfully submitted that the rejection of the pending claims under 35 U.S.C. § 103(a) should be reversed.

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[1] The Cheng article states at Table II that the given number is the "Mean (± SD; n = 6)..."

[2] See "Pharmaceutical Statistics: Practical and Clinical Applications"; 4th Ed., edited by Sanford Bolton and Charles Bon, 2004, pages 19-21. If the Board desires, Appellants will submit a copy of this reference for the Board's review.

[3] The pharmacokinetic data in the Cheng et al. article reports the total HMG-CoA reductase inhibitors concentration, which includes metabolites, rather than the total drug concentration. Therefore, the reported pharmacokinetic data in the Cheng article is different from the data contained in the subject application.

REPLY TO DOUBLE PATENTING REJECTION

In addition to the reasons of record, Appellants respectfully submit that the pending claims are not obvious variations of the claims of United States Patent No. 6,485,748 because the pending claims require a T_{max} of 10 to about 32 hours. As explained above, Appellants' sustained release statin dosage form that exhibits T_{max} of 10 to about 32 hours results in an increase in total statin concentration in the patients blood and lower peak level of the active acidic metabolite. These unexpected properties correspond to more drug being available for treatment and less risk of toxicity to the patient's muscles. None of the cited references of record disclose or suggest a statin dosage form that exhibits a T_{max} of 10 to about 32 hours and therefore none of the references of record disclose or suggest a dosage form as recited in the pending claims with the superior and unexpected properties obtained by Appellants.

If the double patenting rejection is maintained but allowable subject matter is found in the pending claims, Appellants are willing to submit a terminal disclaimer with respect to United States Patent No. 6,485,748 to overcome the double patenting rejection.

CONCLUSION

Based on the above, Appellants respectfully submit that the pending claims are patentable over the cited prior art and that the rejections of the Examiner properly are reversed. Favorable action is respectfully requested and earnestly solicited.

Respectfully submitted,

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